REMARKS

This document is submitted in response to the final Office Action dated September 9, 2008 ("Office Action").

Applicant has amended claim 1 to promote clarity. No new matter is introduced.

The amendment should be entered as it raises no new issues that will require further consideration or search and also does not touch the merits of the application within the meaning of 37 C.F.R. § 1.116(b).

Claims 1-4 and 6-21 are pending. Among them, claims 2-4, 6-10, 12, 13, and 18-21 have been withdrawn from consideration and claims 1, 11, and 14-17 are under examination. Note that claim 5 was cancelled previously.

All of the claims being examined are rejected for obviousness on two grounds. Applicant addresses both grounds separately below.

I

Claims 1, 11, and 14-16 are rejected for obviousness over US Patent No 5,877,213 ("Samid"). See the Office Action, page 2, penultimate paragraph.

Claim 1 will be discussed first. This claim covers a method for treating **certain side effects** that were induced by chemotherapy or radiotherapy by administering a histone hyperacetylating agent to a subject in need.[1] It is noteworthy that the side effects to be treated by this method are a direct consequence of chemotherapy or radiotherapy and not from the underlying cancer state itself. In other words, claim 1 does not aim at treating cancer, as mistakenly believed by the Examiner.

Samid teaches compositions and methods for treating anemia, cancer, AIDS, or severe β-chain hemoglobinopathies by administering a therapeutically effective amount of phenylacetate and its derivatives, e.g., phenylbutyrate (a histone hyperacetylating agent). See Samid, Abstract.

---

[1] Applicant has removed the term "tumorigenesis" from claim 1 to avoid any possibility that this claim would be interpreted as directed to cancer treatment. Applicant has chosen not to amend the preamble of claim 1, which reads "A method for increasing therapeutic gain in chemotherapy or radiotherapy" as this claim specifies that "therapeutic gain" refers to certain side effects induced by chemo/radiotherapy. However, Applicant leaves it to the Examiner's discretion to amend the current preamble to "A method for treating side effects caused by chemotherapy or radiotherapy," if necessary.

The Examiner concludes that "it would have been *prima facie* obvious ... to administer sodium phenylbutyrate [NaPB] in the manner prescribed by Samid, in combination with radiotherapy, as a method of treating tumorigenesis[,]" thereby arriving at the method of claim 1. See the Office Action, page 3, lines 14-16. Applicant respectfully disagrees and would like to point out that, for the following reasons, Samid, in fact, teaches away from combining NaPB with radiotherapy.

Using sodium phenylacetate (NaPA) as an example, Samid teaches that NaPA and its derivatives (e.g., NaPB) are effective in treating cancer. See Abstract. More specifically, it points out that NaPA treatment resulted in concentration-dependent cell growth arrest. See column 14, lines 31-32 and Figure 4; emphasis added. This reference further teaches that "2-4 mg/ml of NaPA...cause a significant inhibition of growth to primary human skin FS4 fibroblasts." See column 17, lines 25-28; emphasis added. In view of these teachings, a skilled person in the art would have readily known that NaPA and derivatives thereof (e.g., NaPB) would aggravate skin tissue damage by inhibiting skin cell growth.[2] As it is commonly known that radiotherapy induces tissue damage, in particular, damage to the epithelial surfaces of the skin, he or she would have been discouraged by the above-noted teachings in Samid from combining NaPA or NaPB with radiotherapy to treat a cancer patient as doing so would worsen the patient's skin tissue damage induced by the radiotherapy.

For the foregoing reasons, Applicant submits that a skilled person in the art, in view of Samid, would not have been motivated to apply both NaPB and radiotherapy to a cancer patient, thereby arriving at the method of claim 1. In other words, a *prima facie* case of obviousness has not been established in the present case.

---

[2] The Samid reference states that NaPA and its derivatives might have potential clinical use in wound healing, referring to FIG 13. See column 11, lines 49-52. The credibility of this statement is questionable for two reasons. First, according to Samid, this statement is supported by FIG 13; however, there is no FIG 13 presented in Samid. In other words, this statement has no factual support. Second, this statement contradicts the other teachings in Samid; namely, NaPA promotes cell death and inhibits skin cell growth, thereby exacerbating tissue damage. As noted above, the other teachings are supported by convincing experimental data. In view of these two reasons, a skilled person in the art would have accepted the other teachings in Samid and disregarded the statement at issue.

Even if it would have been *prima facie* obvious to combine NaPB with radiotherapy (which Applicant does not concede), the obviousness can be overcome by the unexpected results presented in the specification. Applicant elaborates on this point below.

As set forth in MPEP § 2145, an applicant can rely on evidence showing that the claimed invention yields **unexpectedly** improved properties or properties not present in the prior art to rebut an obviousness rejection. Further, the law is well settled that "[w]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the **closest prior art**." See *Pfizer v. Apotex*, 480 F.3d 1348, 1370 (Fed. Cir., 2007); emphasis added.

In the present case, Samid, the reference relied on by the Examiner, is clearly the **closest prior art**. As pointed out above, this reference suggests that a histone hyperacetylating agent, i.e., NaPB, inhibits skin cell growth, thereby **aggravating skin tissue damage**. By contrast, the present specification teaches that a histone hyperacetylating agent promotes cell growth and facilitates **healing** of damaged tissues. For example, Example 3 therein discloses that a number of histone hyperacetylating agents, e.g., phenylbutyrate, alleviated tissue damage induced by radiation. See page 22, line 14 through 23, line 29. As another example, Example 13 discloses that phenylbutyrate facilitated recovery from mucositis (i.e., **healing** of tissue damage of mucous membranes) induced by either radio- or chemo-therapy. See page 32, line 20 through page 34, line 14 and Table 4. Compared to the **closest prior art**, i.e., Samid, the **healing** effect of a histone hyperacetylating agent disclosed in the specification is clearly **unexpected**. This **unexpected** effect is the outcome of the method of claim 1, i.e., administering a histone hyperacetylating agent to a subject.[3] Pursuant to the guideline

[3] Applicant would like to point out a difference between the method of claim 1 and the teachings in Samid. In addition to cancer patients, the claimed method can also target non-cancer patients who suffer from side effects induced by chemo- or radio-therapy, given the healing effect of the histone hyperacetylating agent used therein. In contrast, Samid teaches use of NaPB, a histone hyperacetylating agent, for treating only cancer patients. In other words, different from the method of claim 1, the Samid treatment cannot be applied to non-cancer patients.

and the *Pfizer* ruling quoted above, the just-noted **unexpected** effect renders claim 1 non-obvious over Samid.

In view of the above remarks, claim 1 is not obvious over Samid. Nor are claims 11 and 14-17, all of which depend from claim 1.

II

Claims 1 and 17 are rejected for obviousness over Samid in view of Shufeng et al., *Investigational New Drugs*, 20:281-295 (2002) ("Shufeng"). See the Office Action, page 3, final paragraph.

As pointed out above, claim 1 is not obvious over Samid for two reasons: (1) Samid teaches away from combining a histone hyperacetylating agent with radiotherapy, which arrives at the method covered by claim 1, and (2) the unexpected healing effect of histone hyperacetylating agents renders claim 1 non-obvious.

Shufeng teaches the use of an anti-cancer drug 5,6-dimethylxanthenone-4-acetic acid (DMXAA), either alone or in combination with other chemotherapeutic drugs, to treat cancer. See Shufeng, Abstract. This reference has nothing to do with histone hyperacetylating agents, let alone suggests use thereof for treating cancer. Thus, in view of the teachings in Shufeng, a skilled artisan would not have been motivated to combine a histone hyperacetylating agent with radiotherapy to treat cancer. In other words, Shufeng does not cure the deficiency of Samid (see reason 1 above).

Even if a skilled person in the art would have had the motivation noted above, Applicant submits that, for the same reasons set forth at page 8 above, claim 1 is still non obvious over Samid and Shufeng in view of the unexpected healing effect also discussed at page 8.

In sum, Samid and Shufeng do not render claim 1 obvious; nor do they render obvious claim 17, which depends from claim1.

CONCLUSION

In view of the above remarks, Applicant respectfully requests that the Examiner withdraw this rejection and place the present application in condition for allowance.

It is believed that all of the pending claims have been addressed. However, the absence of a reply to a specific rejection, issue or comment does not signify agreement with or concession of that rejection, issue or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

No fee is believed to be due. Please apply any charges to Deposit Account No. 50-4189, referencing Attorney Docket No. 55701-004002.

Respectfully submitted,

Date: 11/10/08

Y. Jenny Chen, Ph.D., J.D.
Reg. No. 55,055

Customer No. 69713
Occhiuti Rohlicek & Tsao LLP
10 Fawcett Street
Cambridge, MA 02138
Telephone: (617) 500-2511
Facsimile: (617) 500-2499